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REVIEW

Comparison of Gustatory Transduction Mechanisms in Vertebrate Taste Cells

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INTRODUCTION

Animals in various classes of vertebrates live in different environments, such as the water, the underground, the surface of lands or the sky, and eat different types of foods. Therefore, it is supposed that various vertebrates have different sensitivities to a variety of chemicals.

Investigations of gustatory transduction mechanisms in taste cells have been carried out with varying vertebrate species, such as catfish, frog, mudpuppy, salamander, mouse, rat, gerbil and hamster. Comparison of gustatory research data obtained in different species of vertebrates must be done carefully because their living environments and food customs differ from each other. When an interpretation of the experimental data obtained from the taste nerve in some animal is given on the basis of taste cell functions, the taste cell data from the same or similar species should be used. Some confusion may happen when the properties of gustatory neural responses in one species are explained by the properties of the taste cell responses in a quite different species. Some researchers confuse an understanding of gustatory nerve and cell data because of citing unadequate references.

In this review we attempted to compare gustatory transduction mechanisms obtained in various mammalian taste cells (rat, mouse, hamster) and amphibian taste cells (frog, salamander, mudpuppy), which were mostly studied with microelectrode techniques and patch electrode techniques. Although there are many review articles which mentioned gustatory transduction mechanisms [9, 30, 41, 43–45, 47, 84], few have carefully compared those in different vertebrates [9, 45].

GUSTATORY TRANSDUCTION IN FROG TASTE CELLS

1. *Characteristics of taste cell responses*

Several species of frogs and toads have been used for investigation of taste mechanisms. Figure 1 illustrates receptor potentials in frog taste cells induced taste stimuli [92]. Figure 2 shows relationships between stimulus concentration

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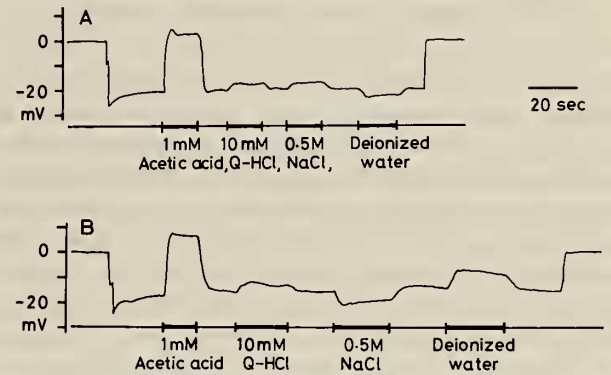

FIG. 1. Intracellular receptor potentials of a frog taste cell in response to acetic acid, quinine-HCl (Q-HCl), NaCl and deionized water. Record A is from a taste cell of the apical region and record B from a taste cell of the proximal region of the tongue. The vertical deflection at the left shows a penetration of taste cell and that at the right a withdrawal of the cell. From [92].

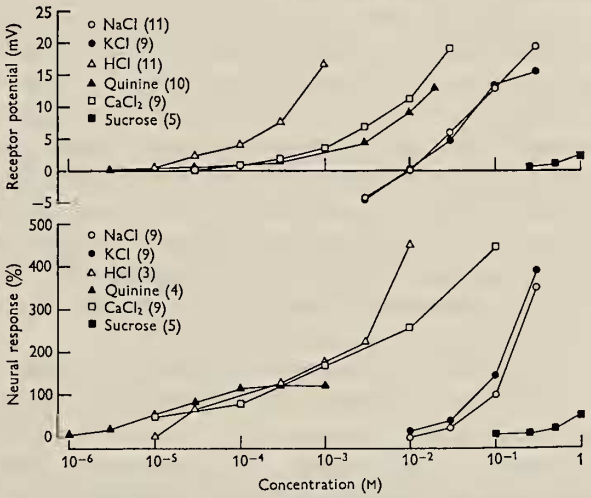

FIG. 2. Relationships between taste stimulus concentration and response magnitude, obtained from the frog taste cell (upper graph) and from the frog glossopharyngeal nerve (lower graph). Stimuli were indicated by different symbols. Each point represents the mean value of the maximum magnitude of receptor potentials and gustatory neural responses obtained from several experiments, the number of which is indicated by a numeral inside a parenthesis after each stimulus. In all the experiments taste receptors were preadapted to 0.01 M-NaCl before each stimulation. From [4].

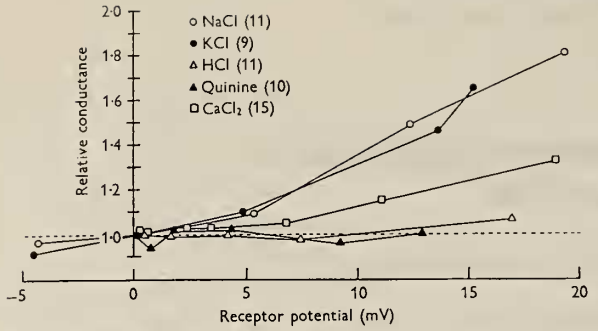

Fig. 3. Relationships between the receptor potential amplitude and the relative conductance magnitude in frog taste cells. The latter represents the ratio of the electrotonic potential magnitudes between rested and stimulated state. Numeral inside the parenthesis is number of taste cells sampled. From [4].

and response magnitude in gustatory cells (upper) and in gustatory nerves (lower) [4]. Salt, bitter and acid stimuli elicit large responses in both gustatory cells and nerves, but sweet stimuli elicit small responses. Intracellular receptor potentials in response to four basic taste stimuli and water stimulus are depolarizing or hyperpolarizing. However, depolarizations are dominant for salt, acid and bitter stimuli. Depolarization in response to water is found in the taste cells in the proximal region of the tongue [92] (Fig. 1). Conductance change during generation of receptor potentials is shown in Figure 3 [4]. Conductance is increased for salt, acid and sucrose but reduced slightly for quinine-HCl (Q-HCl) [4, 53, 69, 87, 97]. The conductance change during water stimulation shows two types [72]: reduction or increment depending on cell types. Frog taste cells can produce spike potentials in response to electrical stimulation [5, 54, 56].

Frog and toad taste organs on the dorsal surface of the tongue are located on the top of the fungiform papillae. Each fungiform has a large disc-shaped structure of 100–300 μm in diameter which is termed the taste disc rather than the taste bud. There are several types of taste disc cells. Classification and nomenclature of the disc cells are controversial [31, 36, 80, 116]. Usually two types of taste cells are distinguished depending on their structure. All the taste cells are innervated by the glossopharyngeal nerves. There are gap junctions between supporting cell and taste cell and between taste cells in the taste disc [86].

In frog taste cell membrane, voltage-gated ion channels (several types of K^+ channels, Na^+ channel, Ca^{2+} channel) and ligand-gated ion channels (Na^+ channel, K^+ channel, non-selective cation channel, Cl^- channel) are found. However, their physiological functions in gustatory transductions are unclear and under investigation [5–8, 25–27, 54–58, 60, 75].

Recently, most studies on gustatory transduction mechanisms in frog taste cells are carried out in our laboratory with microelectrode and patch pipette techniques. Therefore, studies on anuran amphibians are focused on our experimental data.

2. Salt taste

The taste cell membrane can be divided into the apical receptive membrane exposed to the oral cavity and the basolateral membrane. The former is usually bathed in the superficial fluid (SF) and the latter in the interstitial fluid (ISF). The amplitudes of the receptor potentials in frog taste cells induced by salt stimuli are greatly decreased when interstitial Na^+ and Ca^{2+} are replaced with choline$^+$, tetramethylammonium$^+$, tetraethylammonium$^+$ [55, 59, 87, 90, 93]. Addition of 5 mM Co^{2+} and 3 μM tetrodotoxin (TTX) to ISF does not affect the receptor potentials. This indicates that TTX-insensitive cation channels in the basolateral membrane play an important role in generation of the receptor potentials [55].

After the normal ionic composition of SF and ISF of the frog tongue is changed with low-concentration Na^+ saline, the relationships between membrane potentials and receptor potentials in a frog taste cell evoked by various concentrations of NaCl and various types of salts can be analyzed to examine the permeability of the taste-receptive membrane to cations and anions (Fig. 4). In this situation, the mean reversal potentials for depolarizing potentials of a taste cell in response to 0.05, 0.2, and 0.5 M NaCl are -40.0, 6.4, and 28.8 mV, respectively [59]. When adding an anion channel blocker, SITS (4-acetamide-4′-isothiocyanostilbene-2,2′-disulfonic acid), to a NaCl stimulus, the reversal potential for receptor potential with NaCl plus SITS becomes about twice larger than that with NaCl alone [59]. This result indicates that Na^+ and Cl^- of the NaCl stimulus permeate the apical receptive membrane. Previously Akaike and Sato [3] suggested that cation and anion of salt stimuli directly permeate the receptive membrane in frog taste cells.

Reversal potentials for 0.2 M NaCl, LiCl, KCl, and NaSCN in frog taste cells are 6.4, 25.4, −1.0, and −7.8 mV, respectively, indicating that permeability of the apical taste receptive membrane to cations of the Cl- salts is of the order of $Li^+ > Na^+ > K^+$ and that the permeability to anions of the Na^+ salts is $SCN^- > Cl^-$ [59]. These results indicate that

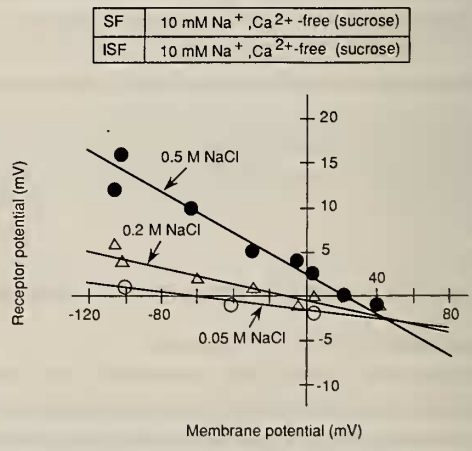

Fig. 4. Relationship between membrane potentials and receptor potentials induced by NaCl stimuli in a frog taste cell. Superficial fluid (SF) and interstitial fluid (ISF) used are shown above the graph. From [59].

the NaCl stimulus-induced receptor potential in a frog taste cell results from an inflow of Na^+ and Cl^- across cation and anion channels on the taste-receptive membrane, as well as an inflow of interstitial Na^+ across cation channels on the basolateral membrane. Salt-induced receptor currents in frog taste cells are recorded with single microelectrode or patch pipette voltage clamping method [58, 73]. Recently, Miyamoto *et al.* found salt stimulus-gated K^+ channels in the frog receptive membrane which show a high permeability to Na^+ [57, 58, 60]. Fig. 5 illustrates a tentative diagram of NaCl signal transduction in a frog taste cell [55, 59, 60].

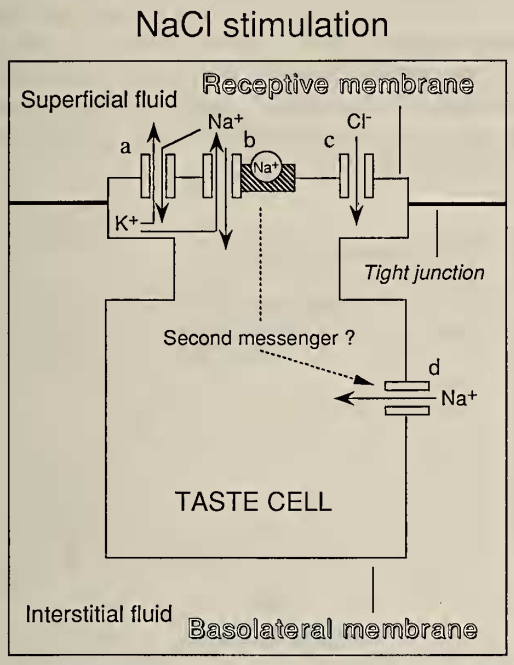

FIG. 5. Schematic drawing of transduction of a NaCl stimulus into receptor potential in a frog taste cell. a, cation channel; b, K^+ channel; c, anion channel; d, cation channel. Voltage-dependent channels, such as Na^+-, K^+- and Ca^{2+}-channels, which are related to generation of spike potentials of the taste cell are removed in this and other figures.

Patch pipette studies with excised patch membranes indicate that there are K^+ channels, nonselective cation channels, and Cl^- channels of various conductances in the apical receptive membrane of frog taste cells [25–27]. However, contribution of these channels to salt signal transduction has not yet been clarified.

Amiloride-blockable Na^+ channels exist in the frog taste cell membrane [8, 55, 66]. Miyamoto *et al.* with *in situ* taste cells could not find a change in NaCl-induced receptor potential following 50 min adaptation of the receptive membrane to 0.1 mM amiloride [55]. Therefore, it is likely that amiloride-blockable Na^+ channels may exist in the basolateral membrane of frog taste cells. The Na^+ channels do not contribute directly to salt signal transduction in frog taste cells.

3. Sour taste

The removal of Na^+, Ca^{2+}, and Cl^- from the normal ISF does not affect the receptor potential in a frog taste cell induced by acid stimuli such as acetic acid and HCl [53]. Interstitial 100 mM K^+ saline also does not affect the acid response [53]. The receptor potential is reduced greatly when Ca^{2+} is removed from the superficial normal saline, but is increased when the Ca^{2+} concentration is elevated [53, 95] (Fig. 6). Similar responses are seen in the frog gustatory nerve [67]. The removal of superficial Cl^- does not affect the receptor potential. The receptor potential elicited by an acid stimulus under superficial Ca^{2+}-free saline is partly caused by Na^+ [53]. Li^+, K^+, NH_4^+, or choline$^+$ substitutes for Na^+ in producing the receptor potential. The receptor potential is unaffected by superficial TTX, but is blocked by superficial Ca^{2+} antagonists such as Co^{2+} and Cd^{2+}. Sr^{2+} and Ba^{2+} substitute for Ca^{2+} in generating the receptor potential [53]. The receptor potentials observed under various concentrations of superficial Ca^{2+} becomes smaller when Na^+ is present in the SF, indicating a competition between Ca^{2+} and Na^+ passing through a Ca^{2+}-permeable conductance in the apical receptive membrane [53].

These findings indicate that a large portion of the recep-

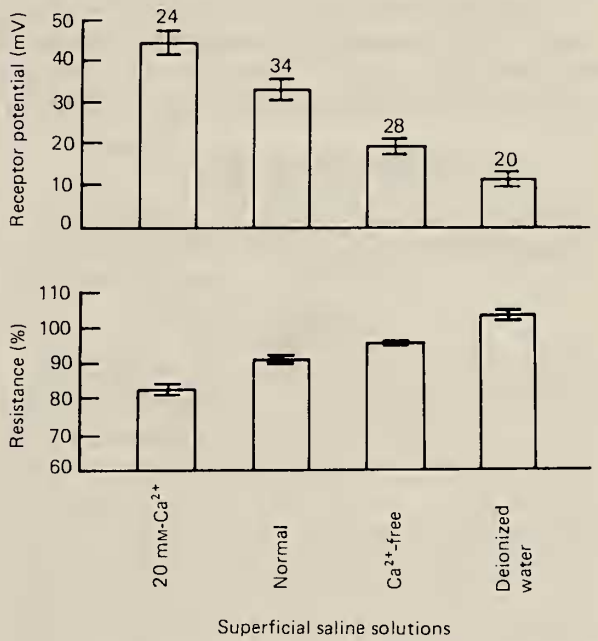

FIG. 6. Relation between the amplitude of receptor potentials and the amplitude of input resistance induced by 1 mM-HCl in frog taste cell. The tongue surface is adapted to 20 mM-Ca^{2+}, normal, Ca^{2+}-free saline solutions and deionized water. The resistance is expressed as a percentage of the control in the unstimulated state. The absolute value of the input resistance in the unstimulated state is 62 ± 6 MΩ with 20 mM-Ca^{2+} saline, 54 ± 5 MΩ with normal (1.8 mM-Ca^{2+}) saline, 53 ± 7 MΩ with Ca^{2+}-free saline and 64 ± 7 MΩ with deionized water. No significant differences are found in any pairs of these figures. From [53].

tor potential induced by acid stimuli is concerned with proton-gated Ca^{2+} channels on the taste-receptive membrane [53]. Both divalent (Ca^{2+}, Sr^{2+}) and monovalent (Na^+, Li^+, K^+, NH_4^+, choline$^+$) cations can pass through the Ca^{2+} channel. Even after the tongue surface is adapted to pure water, the amplitude of acid-induced response in a taste cell remains as large as 35% of the control (Fig. 6). After 0.1 mM DCCD (N,N'-dicyclohexylcarbodiimide), a proton pump inhibitor, is added to SF, the acid response is greatly suppressed, indicating a contribution of proton transporter on the receptive membrane to the acid-induced receptor potential [74].

The receptor current from a dissociated frog whole taste cell can be recorded with a patch pipette filled with 100 mM CsCl. Application of 0.1 mM acetic acid stimulus containing 80 mM $BaCl_2$ to the cell initiates an inward current of about -50 pA at the holding potential of -40 mV [75]. After the taste-receptive membrane alone is damaged, the receptor current induced by acetic acid stimulus containing the $BaCl_2$ greatly decreases, indicating that the inward receptor current is induced by Ba^{2+} passing across proton-gated Ca^{2+} channels on the apical receptive membrane. Cation permeability of the proton-gated Ca^{2+} channel is: $P_{Ca}:P_{Ba}:P_{Sr}:P_{Na}:P_{Cs}$ $=1.87:1.17:0.73:0.99:1.00$ [75]. Therefore, this channel should be called rather a proton-gated nonselective cation channel than the proton-gated Ca^{2+} channel.

It is concluded that most of the acid-induced response in a frog taste cell is generated by a current carried through the proton-gated cation channel of the apical receptive membrane, and that the remaining portion of the acid response is generated by current carried through a DCCD-sensitive proton transporter of the receptive membrane [53, 74] (Fig. 7).

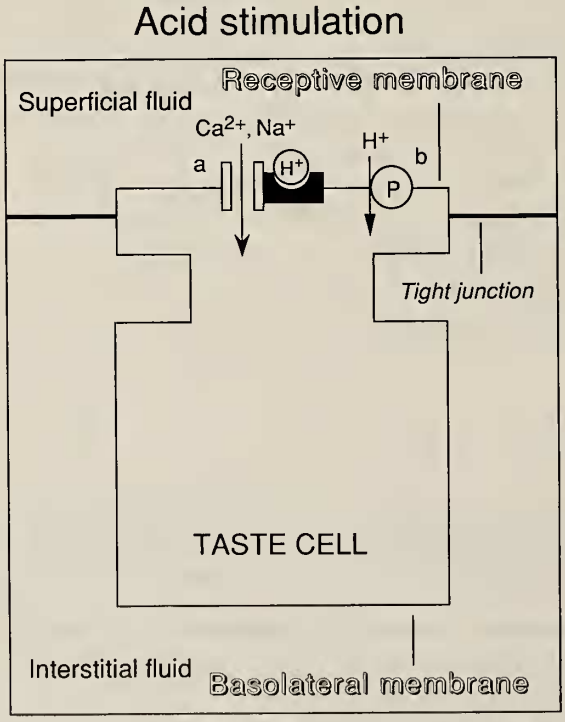

Fig. 7. Schematic drawing of transduction of an acid stimulus into receptor potential in a frog taste cell. a, proton-gated nonselective cation channel; b, H^+-transporter.

4. Bitter taste

The ionic mechanism of the receptor potential in a frog taste cell elicited by quinine-HCl (Q-HCl) has been studied. The frog taste cells whose receptive membranes are adapted to normal saline and deionized water generate depolarizing receptor potentials at Q-HCl concentrations higher than 2 and 0.01 mM, respectively [69]. The input resistance of the taste cell during Q-HCl stimulation increases slightly [4, 69, 97]. The receptor potential does not change even when the membrane potential level is greatly changed. The magnitude of the receptor potential is increased by reducing the concentration of superficial Cl^- on the taste-receptive membrane (Fig. 8), but is independent of the concentration of superficial Na^+ [69, 97].

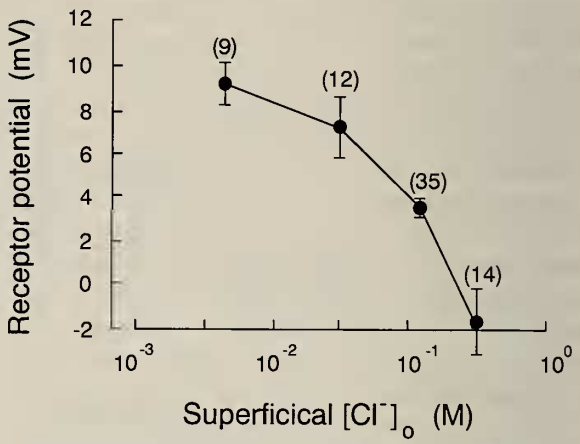

Fig. 8. Relationship between concentration of superficial Cl^- and amplitude of Q-HCl-induced responses in frog taste cells. Numerals in parentheses are numbers of taste cells sampled. From [69].

Injection of Cl^- into a frog taste cell greatly increases the receptor potential [69]. The magnitude of the receptor potential is greatly decreased by removing interstitial Na^+ or Cl^-, or both, surrounding the basolateral membrane of the taste cell. Furosemide (1 mM) added to the ISF decreases the receptor potential to 15%, while interstitial ouabain (0.1 mM) and superficial SITS (0.1 mM) do not influence it [69, 97]. From these results, we can conclude [69, 94, 96, 98]: (1) an electroneural Na^+/Cl^- cotransport occurs through the basolateral membrane of a frog taste cell in the resting state, so that Cl^- accumulates inside the cell. (2) Q-HCl stimulation induces the active secretion of Cl^- across the taste receptive membrane, resulting in a depolarizing receptor potential (Fig. 9).

5. Sweet taste

The frog taste cell generates a depolarizing receptor potential accompanying a remarkable reduction of input

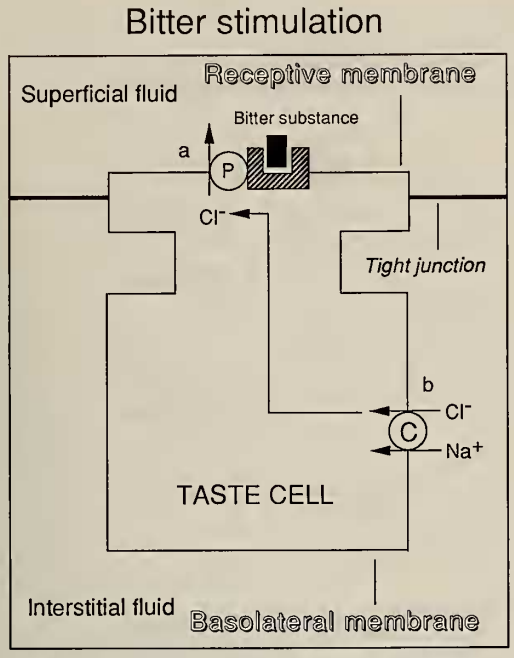

FIG. 9. Schematic drawing of transduction of a bitter stimulus into receptor potential in a frog taste cell. a, Cl^- pump; b, electroneutral Na^+/Cl^- cotransporter.

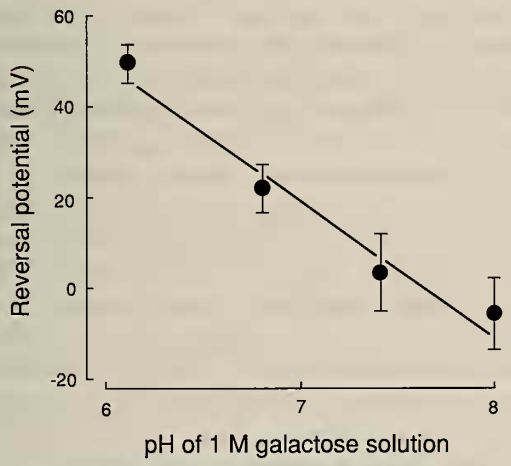

FIG. 10. Relationship between pH of 1 M galactose and reversal potential for receptor potentials in frog taste cells. Points are means from three or four taste cells; bars are SE. From [71].

resistance in response to stimulation with galactose and sucrose [71]. The magnitude of the receptor potential in response to a galactose solution increases linearly with decreasing pH in the pH range 6–8, but remains constant above pH 8 [71]. The reversal potential is increased by only 29 mV by a 10-fold increase in the H^+ concentration of the stimulus, suggesting that there are pH-dependent and pH-independent components in the mechanism generating the receptor potential [71] (Fig. 10). Superficially added blockers of anion channels (0.1 mM SITS) have no effect on the receptor potential. Na^+-free, Ca^{2+}-free, and K^+-free ISF do not affect the receptor potential, but the elimination of Cl^- from the ISF largely abolishes it [71]. Interstitial 0.1 mM DCCD completely inhibits the receptor potential, and interstitial 0.1 mM N-ethylmaleimide decreases the potential to 40% of the control value [71]. Lowering the pH of ISF from 7.2 to 6.3 greatly decreases the receptor potential. It is concluded that part of the receptor potential in frog taste cells induced by sugar stimuli may be produced by an inflow of H^+ through the taste-receptive membrane [71] (Fig. 11). The intracellular pH of the taste cell may be regulated by a Cl^--dependent H^+ pump in the basolateral membrane [71].

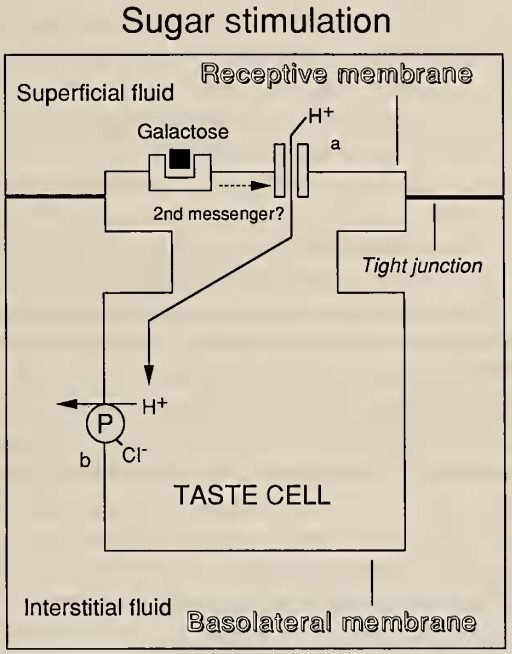

FIG. 11. Schematic drawing of transduction of a sugar stimulus into receptor potential in a frog taste cell. a, H^+ channel; b, Cl^--dependent H^+ pump.

6. *Water taste*

The frog taste cell located in the proximal portion of the tongue generates a depolarizing receptor potential that averages 10 mV in response to stimulation with deionized water [72]. Water-sensitive taste cells are classified into two types: Cl^--dependent and Cl^--independent. In Cl^--dependent cells whose input resistance is decreased or unchanged by deionized water, the magnitude of the water-induced depolarization decreases with an increase in concentration of superficial Cl^- in contact with the receptive membrane and with addition of blockers of anion channels (0.1 mM SITS and 0.1 mM DIDS) to deionized water [72]. The reversal potential for the depolarization in this type shifts according to the concentration of superficial Cl^- [72]. These properties of the responses are consistent with those of the glossopharyngeal nerve, which innervates the taste disc. In Cl^--independent cells whose input resistance is increased by deionized water, the reversal potential is approximately equal to the equilibrium potential for K^+ at the basolateral membrane [72]. The water-induced response of the glossopha-

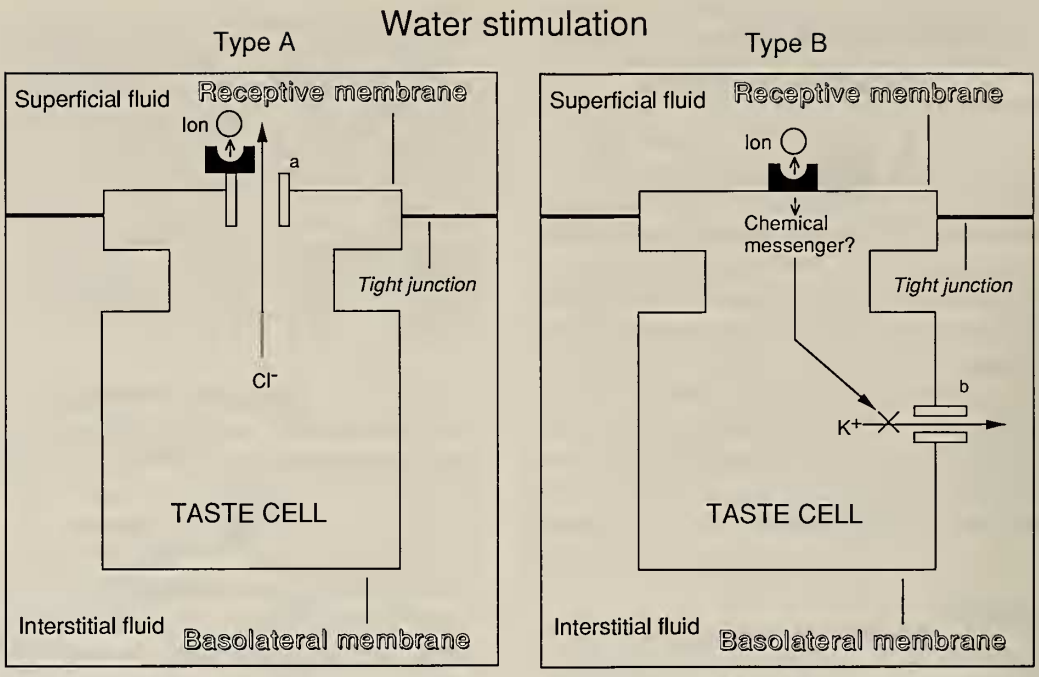

FIG. 12. Schematic drawing of transduction of a water stimulus into receptor potential in frog taste cells. The type A is Cl^--dependent, water-sensitive taste cell, and the type B is Cl^--independent, water-sensitive taste cell. a, Cl^- channel; b, K^+ channel. X means block of channel.

ryngeal nerve is decreased to about 60% of the control value by addition of interstitial 2 mM Ba^{2+}. K^+ channels of approximately 40 pS are found in the frog taste cell membrane [6, 26, 27]. The activities of these channels are blocked by cAMP in the presence of ATP and cAMP-dependent protein kinase [6, 27]. The frog taste cells *in situ* depolarized by intracellular injection of cAMP and cGMP have been found [68]. Probably, the K^+ channels are related to a depolarization of Cl^--independent, water-sensitive frog taste cells, which is accompanied with increase of the membrane resistance. It is concluded that the water-induced receptor potential is produced by Cl^- secretion through the taste-receptive membrane in about 70% of Cl^--dependent, water-sensitive frog taste cells (type A in Fig. 12), while it is generated by an inhibition of the resting K^+ conductance of the basolateral membrane in the remaining 30% of Cl^--independent, water sensitive taste cells [72] (the type B in Fig. 12).

GUSTATORY TRANSDUCTION IN TAILED AMPHIBIAN TASTE CELLS

1. *Cellular organization of taste buds*

In tailed amphibians, taste buds are found over the whole dorsal surface of the tongue [16]. The glossopharyngeal nerve innervates the taste buds. Taste buds contain three types of cells: dark, light and basal cells [82]. The basal cells can be further divided into two types: undifferentiated stem cell and Merkel-like cell [19]. The dark and light cells have an elongated, bipolar structure and are regarded as taste receptor cells which extend apical processes to the taste pore.

2. *Types of ionic channels in taste cells*

Taste cells of the mudpuppy, *Necturus*, are electrically excitable and generate action potential in response to taste stimuli [38, 81]. Some basal cells also possess the action potential [13]. Using the patch-clamp technique, it has been confirmed that taste cells in tailed amphibians possess a variety of voltage-dependent currents, such as a TTX-sensitive Na^+ current, a L-type Ca^{2+} current and several K^+ currents [39, 51, 106]. The role of the action potential is unclear. The action potential may be necessary to activate the Ca^{2+} current underlying a neurotransmitter release. The microelectrode study in mudpuppy taste cells [48] identified a Ca^{2+}-dependent chloride conductance which might terminate the depolarizing responses elicited by taste stimuli [108]. Electrical coupling has been observed between a group of taste cells in mudpuppy taste buds [117]. It is thought that such groups may form an organization unit within taste buds. The taste cell-basal cell synapse also has been identified in a lingual slice preparation [22].

3. *Salty taste*

In whole-cell recordings from taste cells in the tiger salamander, *Ambystoma*, it has been shown that Na^+ influx through amiloride-sensitive Na^+ channels mediates transduction of Na^+ salts into receptor potentials [107] (Fig. 13). Amiloride reduces a sustained Na^+ current in isolated salamander taste cells (Fig. 14) and inhibits a NaCl-induced neural response in the animals, suggesting that these channels are located in the apical receptive membrane. The drug, however, does not block the neural response elicited by NaCl in the mudpuppy [50]. Alternatively, an apically-located K^+ channels mediate transduction of K^+ salts in the mud-

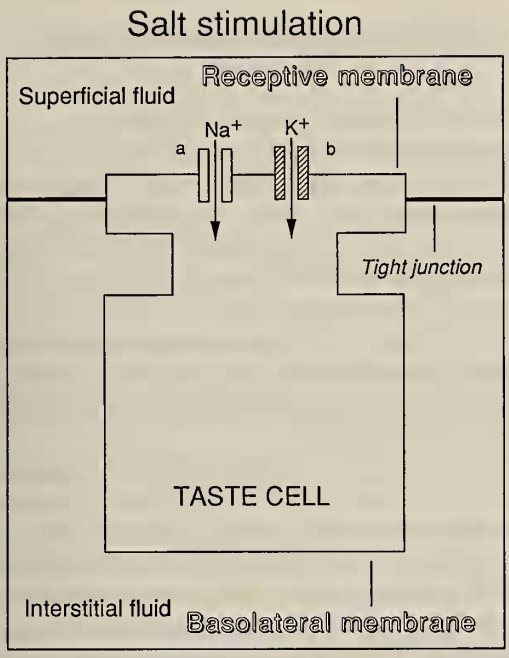

FIG. 13. In tiger salamander, Na^+ ions directly pass through apical amiloride-sensitive Na^+ channels (a). Alternatively, in mudpuppy, K^+ ions also directly pass through apical TEA-sensitive K^+ channels (b).

puppy taste cells [40, 42]. It is likely that K^+ flux through the channel can depolarize taste cells. The dominant sensitivity of K^+ salts in the mudpuppy has already been reported with the microelectrode technique [115].

4. Bitter and sour tastes

In the mudpuppy, block of the apically-located K^+ channels may mediate the transduction of several taste stimuli, including sour, bitter and $CaCl_2$ stimuli (Fig. 15). Patch-clamp and microelectrode studies have shown that these stimuli all reduce the voltage-dependent K^+ current in the mudpuppy taste cells [12, 39, 40]. Since the voltage-dependent K^+ current is restricted to the apical membrane of the taste cells [83], the K^+ channels are directly exposed to taste stimuli. Recent investigation with single channel recording also has indicated that the channels are all blocked by citric acid and quinine applied to outer surface of the channels [17] (Fig. 16). Since these channels exhibit a significant open probability at rest, block of the channels can produce depolarization in taste cells. Similar results have been obtained in the tiger salamander taste cells [107]. The taste cells in the animals, however, generate the inward current accompanied by conductance increase in response to sour stimuli. The blocking mechanism may result in a lack of discrimination among those taste stimuli [14], although single unit analysis of the glossopharyngeal nerve response has suggested the discrimination between the sour and bitter tastes in the mudpuppy [85]. The cross-adaptation analysis of the glossopharyngeal nerve between taste stimuli and K^+ channel blockers still has not been made.

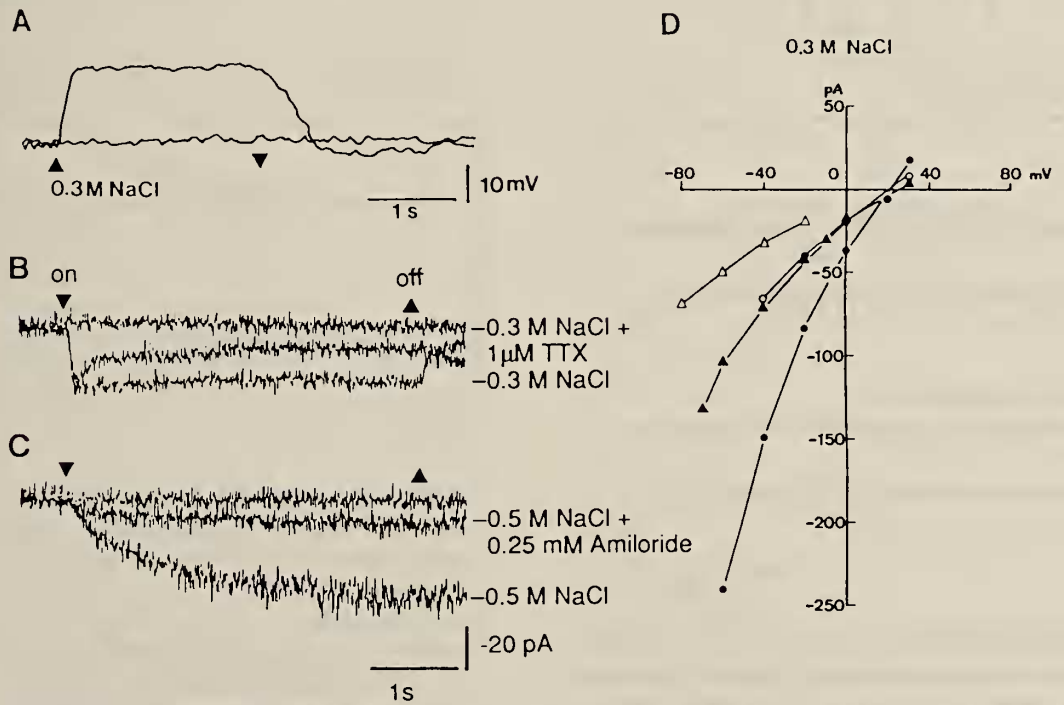

FIG. 14. NaCl-induced taste cell responses in tiger salamander. Application of 0.3 M NaCl induces a depolarization in a current-clamped taste cell (A). 0.3 M NaCl induces a sustained inward current in a voltage-clamped taste cell. The inward currents are partially blocked by TTX (B) and amiloride (C). Effect of holding potential on 0.3 M NaCl-induced inward currents in four taste cells (D). The data are obtained by the whole cell recordings from isolated taste cells. From [107].

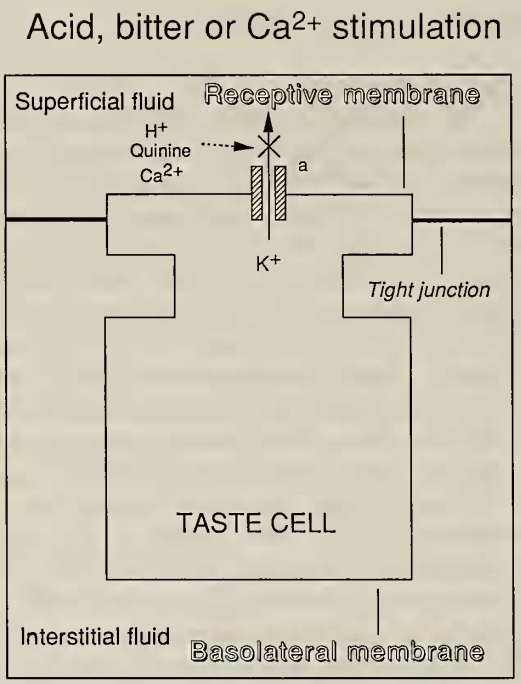

Fig. 15. Schematic drawing of mechanism of transduction of acid, bitter and $CaCl_2$ stimuli into receptor potentials in tailed amphibian taste cells. In tailed amphibians, acids, quinine and Ca^{2+} depolarize taste cells by direct block of apical K^+ channels (a). This diagram comes from [12, 39, 107].

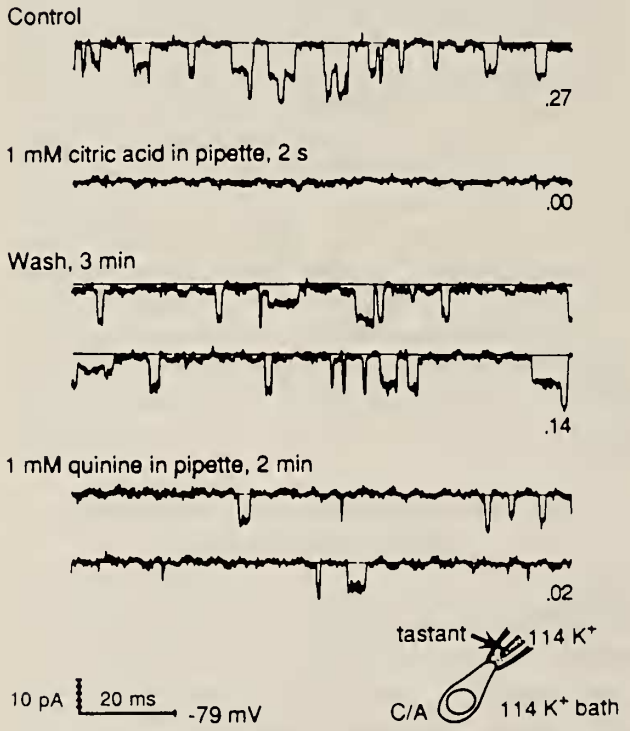

Fig. 16. Effect of citric acid and quinine, applied via pipette perfusion, on apical K^+ channels in a cell-attached patch of a mudpuppy taste cell. Citric acid and quinine block the channels directly. The recording pipette is put on the apical membrane and stimuli are also applied via the pipette perfusion (diagram at the bottom). From [17].

GUSTATORY TRANSDUCTION IN MAMMALIAN TASTE CELLS

1. General properties of gustatory responses

The taste cells are tightly packed in the taste bud. Taste buds in the tongue exist in three types of lingual papillae: fungiform, foliate and vallate. The fungiform papillae are located on the anterior two thirds of the tongue surface and are innervated by the chorda tympani nerve, which has higher sensitivity to salty and sweet tastes. The foliate and vallate papillae are located on the posterior and lateral surfaces of the tongue, respectively and are innervated by the glossopharyngeal nerve, showing higher sensitivity to sour and bitter tastes [79] (Fig. 17).

Ultrastructural observation indicates that four types of taste bud cells, dark (type I), light (type II), intermediate (type III) and basal cells, exist in a taste bud. It is believed that only type III cells which have synaptic contact with the gustatory nerve are gustatory cells, and basal cells situating at the bottom of taste bud are a stem cell of taste cells. Usually, type I, II and III cells excepting basal cells cannot be distinguished from one another by light microscopic figures. In electrophysiological studies with intracellular microelectrodes, taste bud cells are clarified into taste cells and non-taste cells by responsivity to taste stimuli [78]. Taste

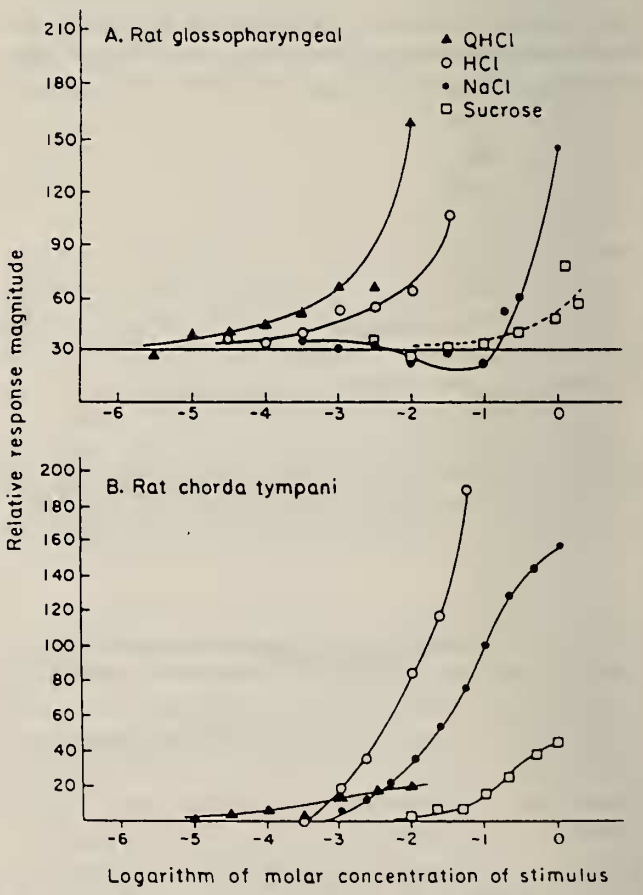

Fig. 17. Comparison of relative response magnitudes for rat glossopharyngeal and chorda tympani nerves. The responses in the two nerves are equated at 1 M NaCl. From [79].

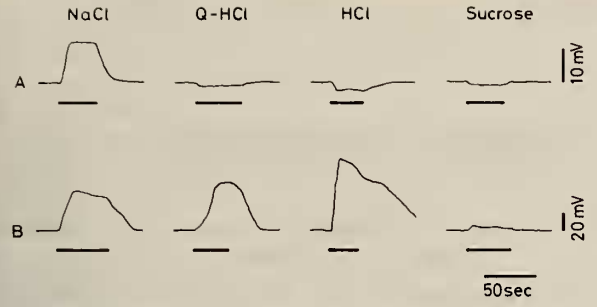

Fig. 18. Intracellularly recorded receptor potentials of rat taste cells in response to four basic taste stimuli. Taste stimuli: 0.5 M NaCl, 0.02 M Q-HCl, 0.01 M HCl, and 0.5 M sucrose. Horizontal bars under the records show the duration of stimulus application. The records A and B are obtained from two taste cells adapted to water. From [91].

cell responses consist of a depolarization, a hyperpolarization and an intermediate response [89, 91, 110, 112] (Fig. 18).

The resting potential and the input resistance of taste cells obtained by an intracellular recording method are −30 to −50 mV and 10 to 300 MΩ, respectively when the cells in rat and hamster are adapted to water [88]. The mean resting potential becomes small when adapted to saline solutions [89]. The whole-cell clamp experiments show that isolated rat taste cells have a zero-current potential of −50 to −70 mV, an input resistance of 1–3 GΩ and a membrane capacitance of 3–5 pF [11]. During gustatory stimulation with basic substances changes in input resistance of rat taste cells are shown in Table 1. The input resistance increases for all stimuli excepting salt stimuli [89, 94].

Table 1. Change in input resistance of rat taste cells at the peaks of receptor potentials elicited by four basic taste stimuli

Taste stimuli	Resistance (%)*	Receptor potential (mV)†	No. of cells
0.5 M NaCl	62±4	25±2	44
0.1 M $CaCl_2$	73±8	24±5	11
0.02 M Q-HCl	178±16	9±2	42
0.01 M HCl	148±8	11±2	34
0.5 M sucrose	138±12	3.4±2.5	26

* The values (mean±SE) are expressed as percent of control input resistance under 41.4 mM NaCl.
† The values are mean±SE under 41.4 mM NaCl adaptaion. From [89].

Spontaneous and tastant-induced firings of action potentials in mammalian taste cells are observed with the patch clamp method [11], but are not with the intracellular recording method [77, 88, 89, 94, 109, 110]. This discrepancy may be partially derived from inactivation of voltage-dependent channels by a damage-induced depolarization by a microelectrode [11]. The role of the action potentials is unclear, but these may be necessary for initiating a transmitter release under a low density of Ca^{2+} channels in mammalian taste cells [11]. At least five kinds of voltage-dependent ionic channels: TTX-sensitive Na^+ channel, transient K^+ channel, outwardly-rectifying K^+ channel, L- and T-type Ca^{2+} channels, and a ligand-dependent channel, amiloride-sensitive Na^+ channel are involved in the rat taste cell membrane [2, 11, 29, 102]. 4-aminopyridine-sensitive, tetraethylammonium-sensitive and cyclic-nucleotide-blockable channels are included in a group of K^+ channels [2, 11, 102].

2. Salty taste

Microelectrode studies suggest that depolarizations in response to salt stimuli are concerned with activation of cation channels accompanied with a decrease of membrane resistance [77, 89, 109]. Schiffman *et al.* [99] first suggested that the amiloride-sensitive Na^+ channels contribute to salty taste transduction in humans. This hypothesis has been supported by many neurophysiological experiments. Amiloride greatly suppresses the chorda tympani nerve responses to NaCl and LiCl, but does not the response to KCl [15, 20, 32, 65]. Recently, localization of amiloride-sensitive Na^+ channel at the apical membrane of taste cells is clarified by noninvasively recording action potentials and currents from a fungiform papilla [10, 28]. Therefore, it is primarily accepted that salt taste transduction occurs through amiloride-sensitive Na^+ channels in mammalian taste cells of the fungiform papillae (Fig. 19). Amiloride-sensitive Na^+ current is confirmed in isolated taste cells of hamster with whole-cell recording (Fig. 20) [29].

Since amiloride can not suppress the whole salt response, the residual salt response is possibly mediated by different

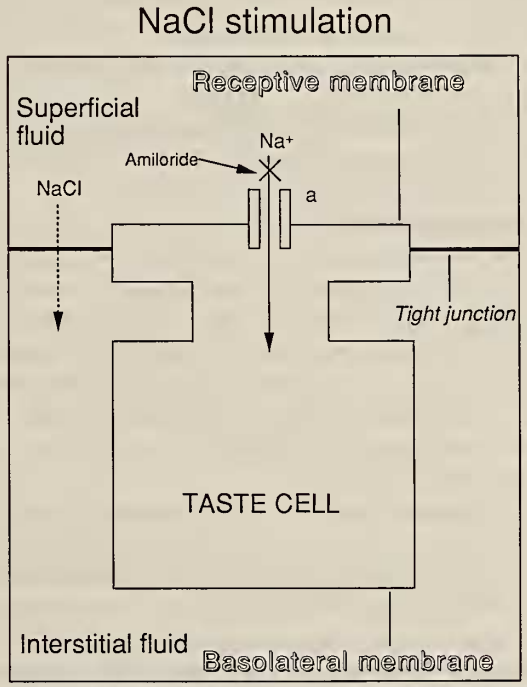

Fig. 19. Schematic drawing of salt signal transduction in mammalian taste cells. Na^+ directly passes through an amiloride-sensitive Na^+ channel (a). Both Na^+ and Cl^- are considered to pass through tight junction from mucosal side to serosal side, resulting in a transepithelial potential change (dotted arrow). From [118].

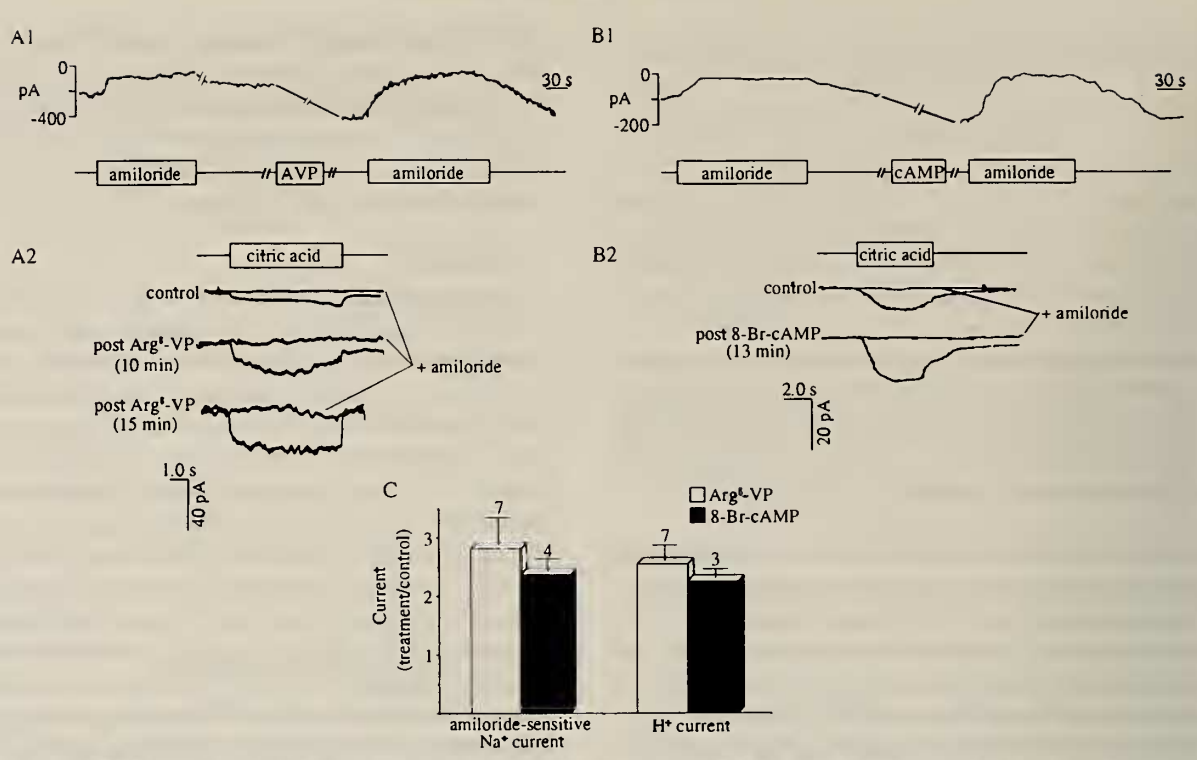

FIG. 20. Suppressive effect of amiloride on response of taste cells isolated from hamster fungiform papillae to citric acid and its enhancement by arginine-vasopressin (Arg^8-VP) and cAMP. Currents blocked by 30 μM amiloride (I_{Na}) are enhanced after treatment with Arg8-VP (AVP) (10 mU/ml for 15 min) (A1) or 0.25 mM 8-bromo-cAMP (cAMP or 8-Br-cAMP) (B1). Current responses to citric acid stimulation ($I_H{}^+$) are also enhanced following treatment with Arg^8-VP (A2) or 0.25 mM 8-Br-cAMP (B2). (C) Mean enhancement of I_{Na} and $I_H{}^+$ by Arg^8-VP and 8-Br-cAMP. From [29].

mechanisms. Amiloride sensitivity of several Na^+ salts is dependent on the size of the anions [23]. However, several anion channel blockers do not affect the salt responses of the chorda tympani nerve [21]. Therefore, Ye *et al.* [118] have proposed a hypothesis that field potentials generated by anion permeability through the pericellular pathway in the taste bud influence salt signal transduction (Fig. 19).

Amiloride-sensitivity of salt responses in the rat chorda tympani changes during development or after Na^+-deprivation [34]. Currents through amiloride-sensitive Na^+ channels in isolated hamster taste cells are enhanced by arginine-vasopressin and cAMP (Fig. 19) [29]. Similar plasticity of NaCl response is known in frog gustatory system [70]. These results suggest a great plasticity in density of amiloride-sensitive Na^+ channels in mammalian taste cells as in other Na^+-absorbing epithelia [114].

The glossopharyngeal nerve in mammals shows a low sensitivity to salts, and the salt response in glossopharyngeal nerve is never affected by amiloride [24]. This indicates that no amiloride-sensitive Na^+ channels are expressed in the taste cells of foliate and circumvallate papillae. The transduction of salt stimuli other than Na^+ salts has not been examined well so far with exception of suppression of KCl response by 4-AP, a potassium channel blocker, in rat chorda tympani nerve [37]. However, other potassium channel blockers such as tetraethylammonium, $BaCl_2$ and quinidine do not reduce KCl response. The suppression of KCl response by 4-AP is 40%. Thus, the mechanism mediating the residual response may be attributed to adsorption of cations and surface potential change on the taste cell membrane after 4-AP suppression [63, 64].

3. *Sour Taste*

For the transduction mechanism of sour taste, no conclusive model has been proposed. It is postulated that in hamster taste cells H^+ included in acid stimuli passes through amiloride-sensitive Na^+ channels, resulting in a depolarization of taste cells [28, 29] (Fig. 19). This hypothesis is consistent with the previous observation in rats [77]. However, amiloride blocks the response to both NaCl and HCl in hamster [33], but does not in monkey [32] and human [99]. Amiloride blocks HCl response in only sodium-selective nerve fiber carrying primarily the information for salty taste in hamster [33] and in rat [65]. Other pathways underlying the transduction mechanism for sour taste stimuli should be pursued in future even if amiloride-sensitive Na^+ channel pathway may play some role in sour taste transduction in mammals.

The decrease of membrane conductance during acid stimuli in rat taste cells has been observed with the intracellular recording method [89]. This might happen if the high density of K^+ channels is localized at the apical membrane [17, 27]. In addition, it should be noted that proton induces an increase of anionic conductance in lingual epithelia, result-

ing in a permeation of small cations in the paracellular pathway [100].

4. Bitter taste

Receptors coupled to G-protein and second messengers are believed to mediate gustatory responses to some bitter substances. Akabas *et al.* [1] have shown that a bitter substance, denatonium, increases an intracellular Ca^{2+} level in some taste cells of the circumvallate papillae in rat. The increased Ca^{2+} is suggested to be released from intracellular Ca^{2+} stores. Biochemical and histochemical studies have shown that IP_3 receptors are present on the endoplasmic reticulum in the apical membrane region of taste cells [35]. Other bitter substances, such as sucrose octaacetate and strychnine, also increase an IP_3 level in mouse taste cells [101]. These data suggest that a bitter substance activates G-protein coupled phospholipase C after binding to the receptor, causing an IP_3 production and a subsequent release of Ca^{2+} from intracellular stores. The released Ca^{2+} may trigger a transmitter release regardless of a depolarization of taste cell membrane (Fig. 21).

Another bitter substance quinine produces a depolarization accompanied by a decrease of the membrane conductance in rat taste cells [77, 89]. Quinine does not induce a Ca^{2+}-release from intracellular stores in taste cells of rat circumvallate papillae [35]. In mouse taste cells, denatonium strongly depresses voltage-dependent outward K^+ currents [102], whereas in rat taste cells denatonium, strychnine and 4-AP do not inhibit voltage-dependent K^+ currents [2]. In guinea-pig taste cells, denatonium does not induce any increase of intracellular Ca^{2+} level [76]. These findings indicate that there may be a species-specific variety in the transduction mechanisms of bitter taste stimuli.

Recently a taste-specific G-protein, gustducin is found, which leads to the activation of phosphodiesterase and in turn decreases the intracellular cAMP concentration [49]. Gustducin is believed to be a possible candidate for the mediator of bitter taste transduction. Amphiphilic substances including bitter and non-sugar sweeteners directly activate G-proteins reconstituted into phospholipid vesicles [62]. Multiple transduction pathways probably exist in bitter transduction mechanisms.

5. Sweet taste

Sweet transduction is related to receptor-mediated mechanisms. Two different models have been proposed to explain the transduction of sweet taste stimuli into a depolarization in taste cells. In the first model [103, 111], binding of sweet molecules to receptor followed by activation of G-

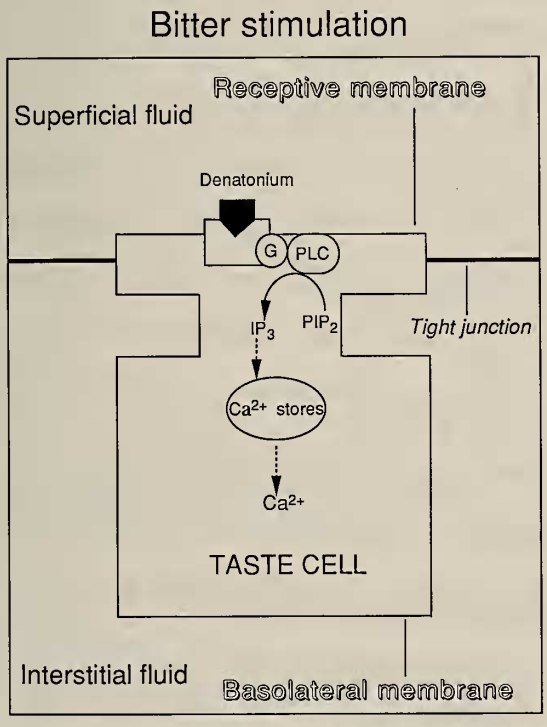

FIG. 21. Schematic drawing of bitter signal transduction in a mammalian taste cell. Bitter substance is thought to have a specific binding site. The formation of bitter substance-receptor molecule complex stimulates IP_3 production via G-protein-coupled PI-turnover. IP_3 induces Ca^{2+}- release from internal Ca^{2+}-stores, and the released Ca^{2+} directly triggers transmitter release without the membrane depolarization. G: G-protein, PLC: Phospholipase C, PIP_2: Inositol 4,5-biphosphate, IP_3: inositol 1,4,5-triphosphate. The data come from [1, 35, 101].

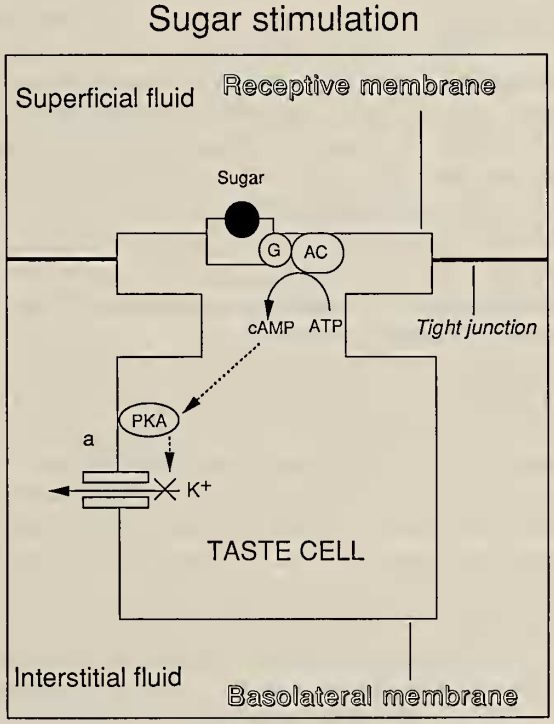

FIG. 22. Schematic drawing of sweet signal transduction in a mammalian taste cell. The binding of sugar to the specific receptor molecule stimulates G-protein-coupled cAMP-production sequence, resulting in activation of a cAMP-dependent protein kinase (PKA). The block (X) of K^+ channels (a) by phosphorylation via PKA induces a depolarization. G: G-protein, AC: Adenylate cyclase, PKA: cAMP-dependent protein kinase. The data come from [103, 111].

protein mediates activation of adenylate cyclase and production of cAMP. cAMP blocks a resting K^+ conductance by activation of protein kinase A, resulting in a depolarization in taste cells (Fig. 22). The second model [52] is that binding of sweet stimuli to receptors opens an amiloride-sensitive cation conductance, leading to a depolarization.

Sucrose induces a decrease or no change of the membrane conductance during depolarizing response in rat [89] and mouse taste cells [110]. Tonosaki and Funakoshi [111] observed a taste cell depolarization in response to an injection of cAMP or cGMP which is accompanied by a decrease of the membrane conductance. Biochemical studies show that sucrose causes a concentration-dependent rise in adenylate cyclase activity in the taste buds of rat [103], pig [61] and cattle [61]. The activation of adenylate cyclase by sucrose stimulation requires the presence of GTP [103] and is blocked by a specific sweet taste inhibitor [104]. Cummings *et al.* (1993) reported that nearly every taste bud responsive to sweeteners also responds to cyclic-nucleotides [18]. These results support the first model. However, biochemical studies indicate that saccharin does not stimulate adenylate cyclase activity in contrast to sucrose [61, 104]. Therefore, it is possible that natural and artificial sweeteners mediate differential transduction mechanisms [62].

Ozeki [77] indicates that sucrose induces an increase of ionic permeability in the rat taste cell membrane because of increase in the membrane conductance. It has been shown that sweeteners induce a short circuit current across the lingual epithelium and amiloride inhibits the chorda tympani response to sweeteners [52]. These results support the second model. The same mechanism is insisted in human sweet taste [99]. In contrast, there are many negative reports in which amiloride or cations in the mucosal solution never affect the responses to sweeteners in mouse [112], hamster [11, 33] or monkey [32]. Amiloride-insensitive conductance located at the basolateral membrane of taste cell may be activated by sugar stimuli.

Recently investigation using northern blot analysis and *in situ* hybridization demonstrates that amiloride-sensitive Na^+ channels are expressed in not only gustatory but also non-gustatory tissue of the lingeal epithelial layer [46]. This means that a large amount of Na^+ is transported from mucosal solution to interstitial fluid through amiloride-sensitive Na^+ channels in taste and non-taste cells when a high concentration of Na^+ is exposed to mucosal side. Tastant is known to induce a secretion of saliva containing more than 10 times the basal concentration of Na^+ [46], and consequently amiloride-sensitive Na^+ channels can modulate the responses to all tastants including sweeteners.

Recently another sweet taste transduction pathway has been proposed with gerbil taste cells [113]. It has been suggested that some sweet amino acids increase intracellular IP_3, and release Ca^{2+} from the internal store, and the released Ca^{2+} may directly release a transmitter substance from taste cells.

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